

**COMBINED DECLARATION AND POWER OF ATTORNEY  
IN PATENT APPLICATION**

Attorney Docket No. AndCIP

As a below named inventor, I, DARRELL R. ANDERSON, NABIL HANNA, JOHN E. LEONARD, ROLAND A. NEWMAN, MITCHELL E. REFF and WILLIAM H. RASTETTER, hereby declare that:

my residence, post office address and citizenship are as stated below next to my name;

I believe that I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled:

THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO  
HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR THE  
TREATMENT OF B CELL LYMPHOMA

the specification of which

(check one) \_\_\_\_\_ is attached hereto.

XXXXX was filed on November 3, 1993 as Application Serial No. 08/149,099. This application is a continuation-in-part of Serial Number 07/978, 891, filed November 13, 1992, now abandoned.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) or patent or inventor's certificate listed below and have also identified below, any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>	<u>Priority Claimed</u> <u>Yes/No</u>
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Serial No.

07/978,891

Filing Date

November 13, 1992

Status (patented,  
pending, abandoned)

Abandoned

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith: Kenneth J. Woolcott, Reg. No. 30,984, and Richard P. Burgoon, Jr., Reg. No. 34,787. Address all telephone calls to Richard P. Burgoon, Jr., at telephone number (619) 550-8680.

Address all correspondence to:

Richard P. Burgoon, Jr.  
Intellectual Property Counsel  
IDEC PHARMACEUTICALS CORPORATION  
11011 Torreyana Road  
San Diego, CA 92121

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-0 Darrell R. Anderson

Full Name of Inventor

United States

Citizenship

1851 Navajo Place, Escondido, CA 92029

Residence

Same as above

Post Office Address

X *Darrell R. Anderson*

Inventor's Signature

April 26, 1994

Date

2-00 Nabil Hanna

Full Name of Inventor

United States

Citizenship

3255 Fortuna Ranch Road, Olivenhain, CA 92024

Residence

Same as above

Post Office Address

X *Nabil Hanna*

Inventor's Signature

April 26, 1994

Date

3-00 John E Leonard United States  
Full Name of Inventor Citizenship

1960 Avenida Joaquin, Encinitas, CA 92024  
Residence

Same as above  
Post Office Address

X John E Leonard April 26, 1994  
Inventor's Signature Date

4-00 Roland A Newman United Kingdom  
Full Name of Inventor Citizenship

4311 Robbins Street, San Diego, CA 92122  
Residence

Same as above  
Post Office Address

X [Signature] April 26, 1994  
Inventor's Signature Date

5-00 Mitchell E Reff United States  
Full Name of Inventor Citizenship

4166 Combe Way, San Diego, CA 92122  
Residence

Same as above  
Post Office Address

X [Signature] April 26, 1994  
Inventor's Signature Date

6-00 William H Rastetter United States  
Full Name of Inventor Citizenship

16067 Puerta Del Sol, Rancho Santa Fe, CA 92067  
Residence

Same as above  
Post Office Address

X [Signature] April 26, 1994  
Inventor's Signature Date

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**Applicant:** ANDERSON, D.R. et al

**Serial No.:** UNKNOWN

**Group Art Unit:** UNKNOWN

**Filed:** HEREWITH

**Examiner:** UNKNOWN

**Title:** THERAPEUTIC APPLICATION OF  
CHIMERIC AND RADIOLABELED  
ANTIBODIES TO HUMAN B  
LYMPHOCYTE RESTRICTED ANTIGEN  
FOR TREATMENT OF B CELL  
LYMPHOMA

3 November 1993  
San Diego, CA

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR  
1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN**

I hereby declare that I am

( ) the owner of the small business concern identified below:

(X) an official of the small business concern empowered to act on behalf  
of the concern identified below:

**NAME OF CONCERN:** IDEC Pharmaceuticals Corporation

**ADDRESS OF CONCERN:** 11011 Torreyana Road  
San Diego, CA 92121

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party of parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled: THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA

by inventors: Anderson, DA; Hanna, N; Leonard, JE; Newman, RA; Reff, ME; Rastetter, WH

described in

- (X) the specification filed herewith  
( ) application Serial No. \_\_\_\_\_, filed \_\_\_\_\_  
( ) Patent No. \_\_\_\_\_, issued \_\_\_\_\_

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below\* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e). \*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME N/A

ADDRESS \_\_\_\_\_

( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING:

Kenneth J. Woolcott

TITLE OF PERSON OTHER THAN OWNER:

General Counsel

ADDRESS OF PERSON SIGNING:

11011 Torreyana Road, San Diego, CA 92121

SIGNATURE



DATE

3 Nov 93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: ANDERSON, DARRELL R., *et al.*

Serial No.: 08/149,099

Group Art Unit:

Filed: November 3, 1993

Examiner:

Title: THERAPEUTIC APPLICATION OF  
CHIMERIC AND RADIOLABELED  
ANTIBODIES TO HUMAN B LYMPHOCYTE  
RESTRICTED DIFFERENTIATION  
ANTIGEN FOR TREATMENT OF B-CELL  
LYMPHOMA

10 January 1994  
San Diego, CA

PATENT ASSIGNMENT

WHEREAS, we, Darrell R. Anderson, a citizen of the United States, residing at 1851 Navato Place, Escondido, CA 92029, County of San Diego, State of California; Nabil Hanna, a citizen of the United States, residing at 3255 Fortuna Ranch Road, Olivenhain, CA 92024, County of San Diego, State of California; John E. Leonard, a citizen of the United States, residing at 1960 Avenida Joaquin, Encinitas, CA 92024, County of San Diego, State of California; Roland A. Newman, a citizen of the United Kingdom, residing at 4311 Robbins Street, San Diego, CA 92122, County of San Diego, State of California; Mitchell E. Reff, a citizen of the United States, residing at 4166 Combe Way, San Diego, CA 92122, County of San Diego, State of California; and William H. Rastetter, a citizen of the United States, residing at 16067 Puerta del Sol, Rancho Santa Fe, CA 92067, County of San Diego, State of California have co-invented a "THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA," for which we have filed application papers for United States Letters Patent thereon, serial number 08/149,099, filed November 3, 1993; and

WHEREAS, IDEC PHARMACEUTICALS CORPORATION, a California Corporation, having a principal place of business at 11011 Torreyana Road, San Diego, CA 92121, is desirous of acquiring the exclusive right, title and interest in the invention and in and to the Letter Patent to be granted and issued therefore throughout the world.

NOW, THEREFORE, for a valuable consideration, the receipt of which is hereby acknowledged; we, Darrell R. Anderson, Nabil Hanna, John E. Leonard, Roland A. Newman, Mitchell E. Reff and William H. Rastetter, do hereby sell, assign, transfer and set over unto IDEC PHARMACEUTICALS CORPORATION, its successors and assigns, the full exclusive right, title and interest in and to the invention, and in and to any and all Letters Patent to be granted and issued therefore, including all continuations, continuations-in-part, and/or divisional applications, not only for, to and in the United States of America, its territories and possessions, but for, to and in all other countries including all priority rights under the International Convention and any other applicable laws or treaties; and we hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to IDEC

PHARMACEUTICALS CORPORATION, its successors and assigns, in accordance with this Assignment.

WITNESS MY HAND at San Diego, California this 11th day of November, 1993.

Darrell R. Anderson  
Darrell R. Anderson

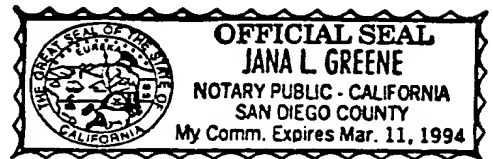
State of California  
County of San Diego

On November 11, 1993, before me, Jana L. Greene, personally appeared Darrell R. Anderson, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature Jana L. Greene  
Jana L. Greene

(Seal)



WITNESS MY HAND at San Diego, California this 11th day of November, 1993.

Nabil Hanna  
Nabil Hanna

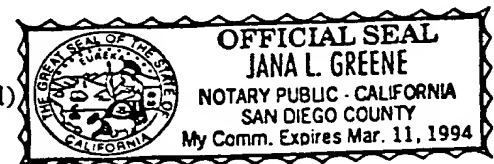
State of California  
County of San Diego

On November 11, 1993, before me, Jana L. Greene, personally appeared Nabil Hanna, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature Jana L. Greene  
Jana L. Greene

(Seal)



WITNESS MY HAND at San Diego, California this 11th day of November, 1993.

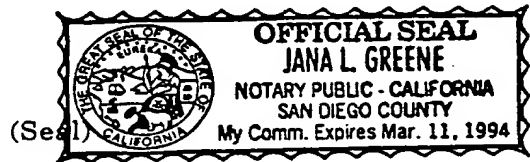
John E. Leonard  
John E. Leonard

State of California  
County of San Diego

On November 11, 1993, before me, Jana L. Greene, personally appeared John E. Leonard, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature Jana L. Greene  
Jana L. Greene



WITNESS MY HAND at San Diego, California this 11th day of November, 1993.

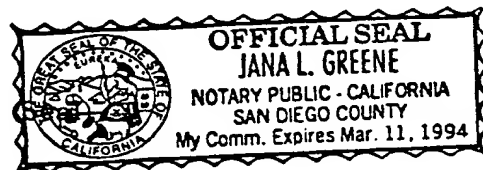
Roland A. Newman  
Roland A. Newman

State of California  
County of San Diego

On November 11th, 1993 before me, Jana L. Greene, personally appeared Roland A. Newman, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature Jana L. Greene  
Jana L. Greene





WITNESS MY HAND at San Diego, California this 11th day of November, 1993.

  
\_\_\_\_\_  
Mitchell E. Reff

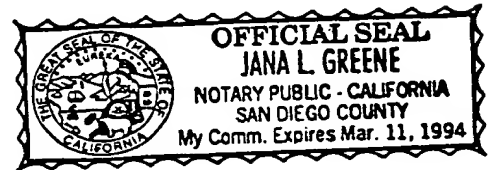
State of California  
County of San Diego

On November 11, 1993, before me, Jana L. Greene, personally appeared Mitchell E. Reff, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

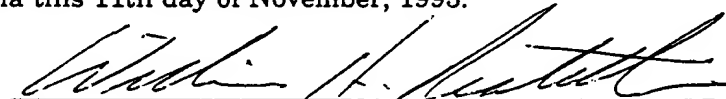
WITNESS my hand and official seal.

Signature Jana L. Greene  
\_\_\_\_\_  
Jana L. Greene

(Seal)



WITNESS MY HAND at San Diego, California this 11th day of November, 1993.

  
\_\_\_\_\_  
William H. Rastetter

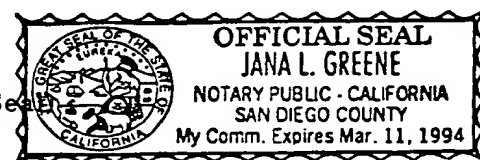
State of California  
County of San Diego

On November 11, 1993, before me, Jana L. Greene, personally appeared William H. Rastetter, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature Jana L. Greene  
\_\_\_\_\_  
Jana L. Greene

(Seal)



865378

# State of California

Be It Known:  
That I, MARCH FONG EU, Secretary of State of the State of California, in the name and by the authority of the People of the State of California, do appoint and commission

JANA L. GREENE

**Notary Public**

of the State of California

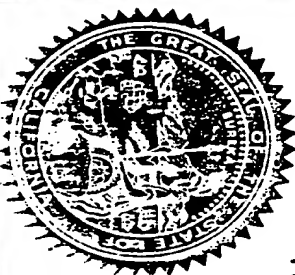
For the term commencing MARCH 12, 1990 and ending MARCH 11, 1994

Principal place of business County of SAN DIEGO

In Witness Whereof, I have hereunto set my hand and caused the Great Seal of the State of California to be affixed at Sacramento,

this NINTH day of MARCH 1990

*March Fong Eu*  
Secretary of State



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE****Applicant:** ANDERSON, DARRELL R.,**Serial No.** 08/149/099**Group Art Unit:** 1805**Filed:** 3 November 1993**Examiner:** Unknown**Title:** THERAPEUTIC APPLICATION OF CHIMERIC AND  
RADIOLABELED ANTIBODIES TO HUMAN B  
LYMPHOCYTE RESTRICTED DIFFERENTIATION  
ANTIGEN FOR TREATMENT OF B-CELL  
LYMPHOMAAugust 31, 1994  
San Diego, CA**PATENT ASSIGNMENT**

WHEREAS, IDEC PHARMACEUTICALS CORPORATION, a California corporation having a principal place of business at 11011 Torreyana Road, San Diego, California 92121, by virtue of an assignment from the co-inventors of United States Letters patent application Serial November 08/149,099, filed November 3, 1993 with the United States Patent and Trademark Office and entitled "THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMAS," said assignment being recorded with the United States Patent and Trademark Office on January 14, 1994, Reel 6850, Frame 0468, has acquired the exclusive right, title and interest in said invention and in and to the Letter Patent to be granted and issued therefore throughout the world.

WHEREAS, MERRILL LYNCH/MORGAN STANLEY ASSOCIATES, L.P., a California Corporation, having a principal place of business at 3000 Sand Hill Road, Building 4, Suite 270, Menlo Park, CA 94025, is desirous of acquiring the exclusive right, title and interest in the invention and in and to the Letter Patent to be granted and issued therefore throughout the world.

NOW, THEREFORE, for a valuable consideration, the receipt of which hereby acknowledged, IDEC PHARMACEUTICALS CORPORATION, does hereby sell, assign, transfer and set over unto MERRILL LYNCH/MORGAN STANLEY ASSOCIATES, L.P., its successors and assignees, the full exclusive right, title and interest in and to the invention, and in and to any and all Letters Patent to be granted and issued therefore, including all continuations, continuations-in-part, and/or divisional, but for, to and in all other countries including all priority rights under the International Convention and any other applicable laws or treaties; and IDEC PHARMACEUTICALS CORPORATION hereby authorizes and requests that the Commissioner of Patents and Trademarks to issue said Letters Patent to MERRILL LYNCH/MORGAN STANLEY, L.P., its successors and assigns, in accordance with this Agreement.

WITNESS MY HAND, at San Diego, California this 31 day of August, 1994.

## IDEC PHARMACEUTICALS CORPORATION



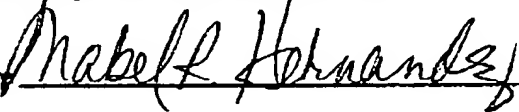
By: William H. Rasetter  
President and Chief Executive Officer

State of California  
County of San Diego

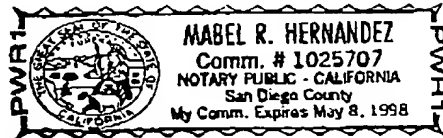
On August 31, 1994 before me, Mabel R. Hernandez, personally appeared William H. Rasetter, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature



(Seal)



WITNESS MY HAND at San Diego, California the 31 day of August, 1994.

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NOTARY PUBLIC OFFICE

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**FIRST DECLARATION UNDER 37 C.F.R. § 1.132**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, do hereby declare:

THAT, an abstract entitled "Immunoreactivity and Effector Function Associated with a Chimeric Anti-CD20 Antibody" was published in The Second Annual IBC International Conference on Antibody Engineering, held December 16-18, 1991 in San Diego, CA and coauthored by Darrell R. Anderson, Robert E. McCoobery, Mitchell Reff, Roland Newman, Syamal Raychaudhuri and Nabil Hanna;

THAT, I am familiar with the claims being considered by the Examiner in the above-identified application;

COPY

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IDEC PHARM MT VW

FAX NO. 6195508754

P. 02

NOV 27 '96 05:16PM BDS&M

P. 1

Application Serial No. 08/149,099  
Attorney's Docket No. 012712-014

THAT, to the extent that the abstract cited above describes the invention claimed in the above-referenced patent application, this article describes my own work and that of co-inventors Mitchell Reff, Roland Newman and Nabil Hanna;

THAT, abstract co-authors Robert E. McCoobery and Syamal Raychaudhuri merely acted under my direction and did not contribute to the conception of the invention disclosed and claimed in the above-referenced patent application;

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/26/96

By: [Signature]  
Darrall R. Anderson

COPY

Patent  
Attorney's Docket No. 012712-014

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of	)	
Darrell R. ANDERSON et al	)	
Application No.: 08/149,099	)	Group Art Unit: 1816
Filed: November 3, 1993	)	Examiner: R. Schwadron
For: THERAPEUTIC APPLICATION	)	
OF CHIMERIC AND RADIO-	)	
LABELLED ANTIBODIES TO	)	
HUMAN B...	)	

**SECOND DECLARATION UNDER 37 C.F.R. § 1.132**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, declare and state as follows:

THAT, I have a Doctorate of Biochemistry from Oklahoma State University;

THAT, a copy of my Curriculum Vitae is attached hereto;

THAT, I am the inventor of the subject matter disclosed and claimed in the above-referenced application and I have reviewed and am familiar with the contents of U.S. Patent Application Serial No. 08/149,099;

THAT, I have reviewed and am familiar with the Examiner's rejection of the claims alleging that the disclosure is purportedly unpatentable over each of Robinson et al. (U.S. Patent Serial No. 5,500,362) and Robinson et al. (WO 88/04936). More specifically, that I understand that the Examiner has concluded that the anti-CD20

COPY

chimeric antibody which is the subject of this application would appear to be functionally equivalent to that disclosed in the above-identified Robinson patent. However, based on the following, I am of the opinion that the Examiner's conclusion is unsustainable as the chimeric anti-CD20 antibody which is the subject of the present invention exhibits properties which were totally unexpected and which moreover render it uniquely suited for use as a therapeutic, in particular for treatment of B cell lymphoma.

THAT, based on the following, I do not agree with the Examiner's conclusion.

THAT, a chimeric anti-CD20 antibody (IDEC-C2B8), consisting of human IgG1-K constant regions was developed by IDEC pharmaceuticals for the treatment of non Hodgkins B cell lymphoma.

THAT, the IDEC-C2B8 antibody lyses CD20+ cells *in vitro* via complement and antibody-dependent cell-mediated lysis.

THAT, preclinical studies have shown that the antibody selectively depletes B cells in blood, lymph nodes and bone marrow in macaque monkeys. Furthermore, the antibody has been shown to be highly effective in treating patients with relapsed low grade lymphoma, producing marked response rates in very sick patients. In my opinion, these clinical results were unexpected and could not have been reasonably predicted based on *in vitro* properties.

THAT, while many of the *in vitro* properties of IDEC-C2B8 are shared with other anti-CD20 antibodies, a remarkable and apparently unique property of IDEC-C2B8 is the ability to deplete CD20 positive cells *in vivo* with such low doses. As low as 0.4 mg/kg was effective in depleting better than 95 percent of B cells in the peripheral blood of



monkeys. This was a surprising result which supports the claims that C2B8 has unique properties beyond what is shared by other anti-CD20 antibodies. While it is difficult to compare directly other chimeric anti-CD20 antibodies because none have been tested *in vivo* as extensively as C2B8, the available evidence would suggest that C2B8 has a much stronger effector depleting property than other chimeric antibodies which is apparently attributable to exceptionally strong Fc receptor binding.

THAT, the following description of an antibody FcRII binding assay conducted under my supervision demonstrates that this enhanced Fc receptor binding is apparently the result of the combining of a unique mouse variable region sequence having a unique amino acid sequence with the human IgG1 constant region:

#### **Binding of IDEC-C2B8 to Human Fc $\gamma$ RII Transfected Cells**

Fc $\gamma$ RII transfected CDW32 cells were attached to a 96 well plate pre-coated with Poly-L-Lysine. Due to the lack of soluble antigen, IDEC-C2B8 and the control antibodies were evaluated in the absence of CD20 by serial dilutions at concentrations ranging from 2 to 0.025  $\mu$ g/mL in wells of the cell coated plate. The amount of antibody bound to the Fc $\gamma$ RII receptors was detected by incubation with Goat Anti-Human IgG-HRP (1:2000) reagent. Peroxidase substrate reagent (TMB) was added and absorbance derived from the color forming reaction was measured at 450 nm with an ELISA plate reader. The results in Figure 1 show that IDEC-C2B8 has exceptionally strong binding to low affinity Fc $\gamma$ RII receptors, in contrast to the positive control human IgG1 isotype and the negative control human IgG4 isotype.

### Conclusion

In my expert opinion, these results are unexpected, in view of the fact that low affinity receptor binding by antibodies is usually reduced in the absence of antigen binding. By contrast, these results indicate that IDEC-C2B8 has an unusually strong affinity for this type of receptor which may be even further enhanced *in vivo* on binding of antigen. The results are highly supportive of the claim that IDEC-C2B8 can mediate effector cell functions *in vivo* with effector cells expressing Fc $\gamma$ RII receptors in a manner unequaled by other CD20 antibodies. Moreover, these results suggest that this antibody does not function equivalently to other chimeric anti-CD20 antibodies.

In my opinion, it would be highly unreasonable to expect that other anti-CD20 antibodies including the chimeric antibodies of the Robinson et al., if compared in this assay, would show equivalent behavior especially because comparison to totally human antibodies of the same isotype as seen in the controls, are not equivalent. In fact, the murine antibody from which the variable region was derived shows no more binding in this assay than the negative control above. Therefore, the subject chimeric antibody shows behavior uncommon to any other antibody tested including other chimeric engineered constructs which differ from C2B8 only in the variable region which is contained therein. This property, therefore, appears to be attributable to the particular variable region contained in the C2B8 antibody. However, it is noted that the assay shown above does not measure or in any way relate to antigen specificity, only the ability to bind to human FcRII receptors. In my opinion, it is this property that is the most unique of the C2B8 effector properties, and may explain the unparalleled ability of the

Application Serial No. 08/149,099  
Attorney's Docket No. 012712-014

subject antibody to mediate such extensive depleting behavior, *in vivo*. As a expert in the art, I can well attest to the fact that type II receptor binding mediated through macrophages and monocytes following specific antibody binding to target cells, is well regarded by many skilled in the art to be the most potent of all possible *in vivo* depleting mechanisms.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11/27/96

By:   
Darrell R. Anderson

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1986 - 1988       Project Scientist, Department of Immunochemistry, Synbiotics  
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1971 - 1972       Decommissioning Supervisor and Troubleshooter, U.S. Naval  
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1967 - 1969       Chief Engineer, U.S. Navy, USS Advance (MSO 510), Long Beach,  
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1982 - 1986       Research Assistant Professor, Department of Biochemistry,  
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**Curriculum Vitae - Darrell R. Anderson****Page 2****Education:**

B.S., Oklahoma State University, Major in Biochemistry, July, 1972

Ph.D. in Biochemistry, Oklahoma State University, Stillwater Oklahoma, December, 1976

**Honors:**

Sigma Xi Graduate Student Research Award for Outstanding Research in the Division of Physical and Biological Sciences. Oklahoma State University, 1976.

NIH Postdoctoral Fellowship 1977-1981.

**Publications:**

1. Anderson, D.A., Grillo-López, A., Varns, C., Chambers, K. and Hanna, N. 1996. Targeted Anti-Cancer Therapy Using Rituximab Chimeric Anti-CD20 Antibody (IDEC-C2B8) in the Treatment of Non-Hodgkin's B Cell Lymphoma. *Trans. Biochem. Society* (in press).
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**Patents:**

- (1993) "Therapeutic Application of Y<sup>90</sup> Labeled Pan B Antibodies to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma," P. Chinn, D. R. Anderson, J. Leonard, and N. Hanna.
- (1991) "Therapeutic Application of Chimeric Antibody to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma," D. R. Anderson, R. Newman, J. Leonard, N. Hanna, and M. Reff.
- (1987) "Method for Early Selection of Internal Image Anti-Idiotypic Antibodies," D.R. Anderson, M. Vodian, and E. Maggio.

**Book Chapters:**

1. Grimes, W.J. and D.R. Anderson. Nutritional Requirements of Animal Cells in Culture. 1981. R. Ham, Ed., *Cambridge University Press*, pp. 388-400.
2. Muller, S., H. Kohler, and D.R. Anderson. Rationale for the Design of Anti-idiotypic Antibody Vaccines in Recombinant DNA Vaccines. 1992. R.E. Isaacson, Ed., *Marcel Dekker, Inc., New York*, pp. 335-367.
3. Anderson, D.R., H. Köhler, and S. Muller. 1992. Biomodulation with Network Epitopes. In *The Biomodulation of Cancer*, M. Mitchell, Ed., *Pergamon Press, Inc. Elmsford, NY*, pp. 155-171.

**Curriculum Vitae - Darrell R. Anderson****Page 4****Recent Abstracts and Presentations:**

**Primatized Antibodies for Repeat Dose Immunotherapy.** *Second International Conference on Commercializing Human Monoclonal Antibodies*, (1994), D.R. Anderson, IDEC Pharmaceuticals Corporation.

**Monoclonal Anti-CD20 Antibody (IDEC-C2B8) Therapy of B-Cell Non Hodgkin's Lymphoma--Pre-Clinical Development and Early Clinical Results.** *NCI-EORTC Meeting (1994), The Netherlands*, A.J. Grillo-Lopez, V. Carrali, J.E. Leonard, B.K. Dallaire, D.R. Anderson, and M.E. Reff.

**IDEC-C2B8: A Promising New Monoclonal Anti-CD20 Antibody for the Treatment of B-Cell Non-Hodgkin's Lymphoma.** A.J. Grillo-Lopez, J.E. Leonard, V. Carrali, B.K. Dallaire, D.R. Anderson, and M.E. Reff.

**Predclinical and Early Clinical Development of the Anti-CD20 Monoclonal Antibody IDEC-C2B8.** *Ninth International Conference on Monoclonal Antibody Imunoconjugates for Cancer, San Diego, CA, March 3-5, 1994*, A.J. Grillo-Lopez, J.E. Leonard, V. Carrali, B.K. Dallaire, D.R. Anderson, and M.E. Reff.

**Regulation of Lymphocyte Activation with PRIMATIZED® Antibodies: Therapeutic Applications in Chronic Autoimmune Diseases.** *IBC's Second Annual Industry Conference; Psoriasis; Latest Advances in Understanding and Therapeutic Development. November 12-13, 1996, Washington, D.C.* D.R. Anderson.

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Patent  
Attorney's Docket No. 012712-014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of )

Darrell R. ANDERSON et al )

Application No.: 08/149,099 )

Filed: November 3, 1993 )

For: THERAPEUTIC APPLICATION OF )  
CHIMERIC AND RADIOLABELED )  
ANTIBODIES TO HUMAN B )  
LYMPHOCYTE RESTRICTED )  
DIFFERENTIATION ANTIGEN FOR )  
TREATMENT OF B CELL LYMPHOMA )

Group Art Unit: 1816

Examiner: R. Schwadron

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Darrell R. Anderson, declare and state as follows:

(1) That I am the same Darrell R. Anderson named as an inventor of the above-identified application.

(2) That I am aware of the facts that led up to the subject invention.

(3) That I am further familiar with the claims being considered by the Examiner in the above-identified application.

(4) That based on such review, and my personal knowledge, I can attest to the fact that William E. Rastetter made an inventive contribution to the subject application. Specifically, William E. Rastetter, Ph.D. was involved in the initial conception relating to the usage of the subject chimeric anti-CD20 antibody as a pharmaceutical for the treatment of B cell lymphoma. Also, Dr. Rastetter was involved in the initial

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Serial No. 08/149,099

Attorney Docket 012712-014

conception relating to the usage of this antibody in combination with a radiolabeled non-chimeric anti-CD20 antibody. Further, I can attest to the fact that the contribution of John E. Leonard solely relates to the combined usage of the subject chimeric anti-CD20 antibody with a radiolabeled non-chimeric (murine) antibody (from which the subject chimeric antibody was derived) as a therapeutic for treatment of B cell lymphoma.

(5) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

5/15/97

Date

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